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Intronless Genes

InvivoGen

## 4-1BB Ligand / CD137 Ligand / TNFSF9

### Co-stimulatory genes

Co-stimulatory molecules are membrane-bound molecules which play a crucial role in T cell activation. Abundantly expressed on antigen presenting cells, co-stimulatory molecules provide a secondary signal to antigen-T cell receptor binding by interacting with independent receptors on T cells. This secondary signal is required to induce T cell proliferation and secretion of cytokines. Co-stimulatory molecules have been used in cancer therapies to increase the immunogenicity of tumor cells and elicit antitumoral immune responses to non-immunogenic tumors. Also, vaccination approaches have benefited from the co-transfer of co-stimulatory molecules with antigens.

### 4-1BBL

4-1BB ligand (4-1BBL) is a membrane protein belonging to the superfamily of tumor necrosis factor (TNF) which provides a co-stimulatory signal to T cells. 4-1BBL is expressed on antigen presenting cells (APCs). 4-1BB, the receptor of 4-1BBL, is present on activated T cells. Interaction between 4-1BB (on T cells) and its ligand (on the APC) increases the activity of both APCs and T cells: APC's proliferation, cell adhesion and/or secretion of various cytokines is elicited, and T cells proliferation is stimulated (Vinay and Kwon, 1998).

Triggering the 4-1BB molecule could provide a treatment for cancer by activating T cells directed against the tumor. Indeed, treatment with antibodies against 4-1BB eradicate established tumors (Melero *et al.*, 1997). Moreover, transduction of 4-1BBL and B7.1 into poorly immunogenic tumor cells induces a systemic antitumoral CTL response (Melero *et al.*, 1998).

	Human Gene	Murine Gene
ORF size	762bp	927bp
Plasmid backbone	pORF	pORF
Subclone with	NcoI - NheI	BspHI - NheI

- Martinet O, Ermekova V, Qiao JQ, Sauter B, Mandeli J, Chen L, Chen SH (2000) Immunomodulatory Gene Therapy With Interleukin-12 and 4-1BB Ligand: Long- Term Remission of Liver Metastases in a Mouse Model. *J Natl Cancer Inst* 92(11):931-936
- Vinay, D.S., and Kwon, B.S. Role of 4-1BB in immune responses. *Sem. Immunol.* 10: 481-489.
- Melero, I., Shuford, W.W., Newby, S.A., Aruffo, A., Ledbetter, J.A., Hellstrom, K.E., Mittler, R.S., and Chen, L. (1997). Monoclonal antibodies against the 4-1BB T-cell activation molecule eradicate established tumors. *Nat. Med.* 3: 682-685.
- Melero, I., Bach, N., Hellstrom, K.E., Aruffo, A., Mittler, R.S., and Chen, L. (1998). Amplification of tumor immunity by gene transfer of the co-stimulatory 4-1BB ligand: synergy with the CD28 co-stimulatory pathway. *Eur. J. Immunol.* 28: 1116-1121.

L15 ANSWER 55 OF 56 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1994:506168 CAPLUS

DOCUMENT NUMBER: 121:106168

TITLE: Comparison of **adjuvant** activities of  
aluminum phosphate, **calcium**  
**phosphate** and stearyl tyrosine for tetanus  
toxoid

AUTHOR(S): Gupta, Rajesh K.; Siber, George R.

CORPORATE SOURCE: Massachusetts Public Health Biol. Lab., State Lab.  
Inst., Jamaica Plain, MA, 02130, USA

SOURCE: Biologicals (1994), 22(1), 53-63

CODEN: BILSEC; ISSN: 1045-1056

DOCUMENT TYPE: Journal

LANGUAGE: English

TI Comparison of **adjuvant** activities of aluminum phosphate,  
**calcium phosphate** and stearyl tyrosine for tetanus  
toxoid

AB The **adjuvant** activity of three adjuvants, aluminum phosphate  
(AlPO<sub>4</sub>), **calcium phosphate** (CaHPO<sub>4</sub>) and stearyl  
tyrosine for tetanus toxoid (TT) were compared to sol. TT in mice at a  
dose of 0.5 Lf (1/10th of the single human dose) and in guinea-pigs at a  
dose of 7.5 Lf (1.5 times the single human dose). Three TT preps.  
varying in purity were used: (1) ammonium sulfate pptd. formalin  
detoxified tetanus toxin (AS-TT); (2) AS-TT ultrafiltered to remove low  
mol. wt. peptides (UF-TT); and (3) chromatog. purified tetanus toxin  
subsequently detoxified with formalin (CP-TT). After primary

immunization

of mice, AlPO<sub>4</sub> adsorbed TTs induced higher toxin-neutralizing and IgG (by  
ELISA) antibodies than CaHPO<sub>4</sub>, stearyl tyrosine adsorbed or sol. TT  
preps., but this difference was no longer present after secondary  
immunization. TT preps. of varying purities showed similar antibody  
responses after primary and secondary immunizations when adsorbed on each  
adjuvant. CP-TT prepn. showed the highest neutralizing antibody level  
amongst sol. preps. after the first dose. All the preps. induced

mainly

IgG1 antibodies. However, stearyl tyrosine adsorbed TT induced

relatively

higher IgG2a and IgG2b responses than AlPO<sub>4</sub>, CaHPO<sub>4</sub> adsorbed or sol. TTs  
particularly after booster **injection**. No prepn. induced  
detectable IgG3 or IgM antibodies. AlPO<sub>4</sub> adsorbed preps. induced higher  
IgE antibodies than CaHPO<sub>4</sub> and stearyl tyrosine adsorbed vaccines. Among  
the sol. preps., CP-TT induced lower anti-TT IgE antibodies than std.  
AS-TT. All these preps. were also tested in the US potency test for  
adsorbed TT in guinea-pigs. While all the preps. passed this test,

AlPO<sub>4</sub>

adsorbed TT preps. induced higher neutralizing and IgG antibodies than  
CaHPO<sub>4</sub> and stearyl tyrosine adsorbed or sol. TT preps. In these animal  
models, purified TT was a strong immunogen and traditional AlPO<sub>4</sub> adjuvant  
gave the highest antibody responses.

L15 ANSWER 56 OF 56 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1979:502174 CAPLUS

DOCUMENT NUMBER: 91:102174

TITLE: Inhibition of cortisone action in mice by heparin

AUTHOR(S): Jokay, I.; Karczag, E.; Kelemenics, K.; Foldes, I.

CORPORATE SOURCE: Microbiol. Res. Group, Hung. Acad. Sci., Budapest,  
H-1529, Hung.

SOURCE: Endokrinologie (1979), 73(2), 199-208

CODEN: ENDKAC; ISSN: 0013-7251

DOCUMENT TYPE:

Journal

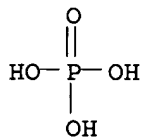
LANGUAGE:

English

AB A single dose of heparin [9005-49-6] applied in a depot-form (Freund's incomplete **adjuvant** or **Ca-phosphate gel**) inhibited the effects of i.p. **injected** cortisone [53-06-5] on the lymphoid organs (thymus and spleen), on the peritoneal and peripheral lymphoid cell count and serum .gamma.-globulin level as well as on liver glycogen deposition in mice. The same dose of heparin did not influence the action of hydrocortisone [50-23-7] measured on thymic and splenic involution and liver glycogen content. The route of cortisone administration seemed to be crit., as heparin showed no or only minor effects when cortisone was given s.c.; moreover, the action of cortisone was more marked by s.c. than by i.p. administration.

=> d his

L1 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2003 ACS  
 RN 10103-46-5 REGISTRY  
 CN Phosphoric acid, calcium salt (8CI, 9CI) (CA INDEX NAME)  
 OTHER NAMES:  
 CN **Calcium phosphate**  
 CN Crodax DP 30  
 CN Dikal 21  
 CN Dynafos  
 CN E 341  
 CN KDV 15u  
 CN LF-CP-ZA  
 CN Man-Gill 51504  
 MF Ca . x H3 O4 P  
 CI COM  
 LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO,  
 CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN,  
 CSNB, DIOGENES, EMBASE, ENCOMPLIT, ENCOMPLIT2, ENCOMPPAT, ENCOMPPAT2,  
 GMELIN\*, IFICDB, IFIPAT, IFIUDB, MEDLINE, MSDS-OHS, PDLCOM\*, PIRA,  
 PROMT, TOXCENTER, TULSA, USPAT2, USPATFULL  
 (\*File contains numerically searchable property data)  
 Other Sources: EINECS\*\*, NDSL\*\*, TSCA\*\*  
 (\*\*Enter CHEMLIST File for up-to-date regulatory information)  
 CRN (7664-38-2)

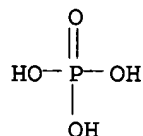


●x Ca

5099 REFERENCES IN FILE CA (1957 TO DATE)  
 100 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA  
 5113 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L1 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2003 ACS  
 RN 7758-87-4 REGISTRY  
 CN Phosphoric acid, calcium salt (2:3) (8CI, 9CI) (CA INDEX NAME)  
 OTHER NAMES:  
 CN .alpha.-Tricalcium phosphate  
 CN .beta.-TCP  
 CN .beta.-Tricalcium phosphate  
 CN .beta.-Whitlockite  
 CN Apamicron AP 12C  
 CN Biphasic calcium phosphate  
 CN Bonarka  
 CN C 13-09SF  
 CN Calcium orthophosphate  
 CN Calcium orthophosphate (Ca3(PO4)2)  
 CN **Calcium phosphate**  
 CN Calcium phosphate (3:2)  
 CN Calcium phosphate (Ca3(PO4)2)

CN Calcium tertiary phosphate  
 CN Cerasorb  
 CN Ceredex  
 CN Multifos  
 CN Ostram  
 CN Phosphoric acid calcium(2+) salt (2:3)  
 CN Posture  
 CN Posture (calcium supplement)  
 CN Synthograft  
 CN Synthos  
 CN TCP  
 CN TCP 10  
 CN Tertiary calcium phosphate  
 CN Tribasic calcium phosphate  
 CN Tricalcium diphosphate  
 CN Tricalcium orthophosphate  
 CN Tricalcium phosphate  
 CN Tricalcium phosphate (Ca<sub>3</sub>(PO<sub>4</sub>)<sub>2</sub>)  
 DR 1344-15-6, 123211-19-8  
 MF Ca . 2/3 H3 O4 P  
 CI COM  
 LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, ACQUIRE, BIOBUSINESS, BIOSIS,  
 BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN,  
 CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DETHERM\*, DIOGENES, DRUGU,  
 EMBASE, GMELIN\*, HSDB\*, IFICDB, IFIPAT, IFIUDB, MEDLINE, MRCK\*,  
 MSDS-OHS, NIOSHTIC, PDLCOM\*, PHAR, PIRA, PROMT, TOXCENTER, TULSA,  
 USPAT2, USPATFULL, VETU, VTB  
 (\*File contains numerically searchable property data)  
 Other Sources: DSL\*\*, EINECS\*\*, TSCA\*\*  
 (\*\*Enter CHEMLIST File for up-to-date regulatory information)  
 CRN (7664-38-2)



● 3/2 Ca

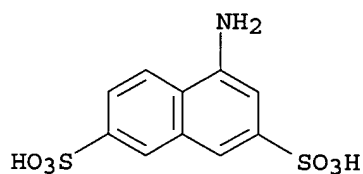
6820 REFERENCES IN FILE CA (1957 TO DATE)  
 107 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA  
 6834 REFERENCES IN FILE CAPLUS (1957 TO DATE)  
 1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS  
 RN 1306-06-5 REGISTRY  
 CN Hydroxylapatite (Ca5(OH)(PO4)3) (9CI) (CA INDEX NAME)  
 OTHER CA INDEX NAMES:  
 CN Hydroxylapatite (8CI)  
 OTHER NAMES:  
 CN Alveograft  
 CN AMDRY 6021  
 CN Apaceram  
 CN APAFILL-G  
 CN Apatite  
 CN Apatite hydroxide (Ca10(PO4)6(OH)2)  
 CN Bonaceram P  
 CN Bonfil  
 CN Calcium hydroxyapatite  
 CN Ceratite  
 CN Durapatite  
 CN FKI  
 CN HAP-B  
 CN Hy-Apatite  
 CN **Hydroxyapatite**  
 CN Interpore 200  
 CN Interpore 500  
 CN Monite  
 CN Supertite 10  
 CN Synamel  
 CN Tri-Tab  
 CN Win 40350  
 DR 12440-80-1, 136841-77-5, 196875-13-5  
 MF Ca . H O . O4 P  
 AF Ca5 H O13 P3  
 CI MNS, COM, TIS  
 LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO,  
 CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS,  
 CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM\*, DRUGU,  
 EMBASE, HSDB\*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK\*, MSDS-OHS,  
 NIOSHTIC, PIRA, PROMT, RTECS\*, TOXCENTER, USAN, USPAT2, USPATFULL  
 (\*File contains numerically searchable property data)  
 Other Sources: DSL\*\*, EINECS\*\*, TSCA\*\*  
 (\*\*Enter CHEMLIST File for up-to-date regulatory information)

Component	Ratio	Component Registry Number
=====+=====		
HO	1	14280-30-9
O4P	3	14265-44-2
Ca	5	7440-70-2

12129 REFERENCES IN FILE CA (1957 TO DATE)  
 342 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA  
 12164 REFERENCES IN FILE CAPLUS (1957 TO DATE)  
 5 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

ER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS  
 RN 6251-07-6 REGISTRY  
 CN 2,7-Naphthalenedisulfonic acid, 4-amino- (7CI, 8CI, 9CI) (CA INDEX NAME)  
 OTHER NAMES:  
 CN 1-Amino-3,6-disulfonaphthalene  
 CN 1-Aminonaphthalene-3,6-disulfonic acid  
 CN 1-Naphthylamine-3,6-disulfonic acid  
 CN 4-Amino-2,7-naphthalenedisulfonic acid  
 CN **Freund acid**  
 FS 3D CONCORD  
 MF C10 H9 N O6 S2  
 CI COM  
 LC STN Files: BEILSTEIN\*, CA, CAOLD, CAPLUS, CHEMCATS, CHEMLIST, IFICDB,  
 IFIPAT, IFIUDB, SPECINFO, TOXCENTER, USPATFULL  
 (\*File contains numerically searchable property data)  
 Other Sources: EINECS\*\*, NDSL\*\*, TSCA\*\*  
 (\*\*Enter CHEMLIST File for up-to-date regulatory information)



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

54 REFERENCES IN FILE CA (1957 TO DATE)  
 54 REFERENCES IN FILE CAPLUS (1957 TO DATE)